Synthesis of 5-Aroylamino-3*H*-1,3,4-thiadiazole-2-thiones and Their Tautomerism

Nam Sook Cho* and Goo Ni Kim

Department of Chemistry, Chungnam National University,
Daejon 305-764, Korea

Cyril Párkányi

Department of Chemistry, Florida Atlantic University,
500 N.W. 20th Street, P.O. Box 3091,
Boca Raton, FL 33431-0991

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5-Aroylamino-3*H*-1,3,4-thiadiazole-2-thiones **2** have been synthesized by acylation of 5-amino-3*H*-1,3,4-thiadiazole-2-thione **1**. 5-Aroylamino-3*H*-1,3,4-thiadiazole-2-thiones can exist in two tautomeric forms - a thiol form and a thione form. On the basis of the ^{13}C nmr spectra and additional experimental information, it has been established that the thione form is the stable form in which these compounds exist.

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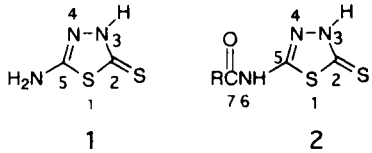
Our long-term continuing interest in thiadiazoles [1-4] forms a part of our systematic efforts to obtain new biologically active pyrimidines, purines, and their analogs. We have earlier reported on the derivatives of 5-amino-2*H*-1,2,4-thiadiazol-3-one [1-3] which is the five-membered ring analog of cytosine, and on the isomeric 5-amino-3*H*-1,3,4-thiadiazol-2-one [1] which is also biologically active [5].

As a continuation of our work in this area, we have turned our attention to 5-amino-3*H*-1,3,4-thiadiazole-2-thione (**1**) which is the sulfur analog of 5-amino-3*H*-1,3,4-thiadiazol-3-one and which was perpared for the first time by Guha [6] by heating of ethanolic solution of potassium thiosemicarbazide dithiocarboxylate under pressure.

A number of 5-amino-3*H*-1,3,4-thiadiazole-2-thiones were obtained as intermediates in the synthesis of the corresponding substituted 5-amino-3*H*-1,3,4-thiadiazole-2-sulfones which find use as pesticides [7,8], 1,3,4-thiadiazolylureas used as herbicides [9-13], and 5-amino-2-benzylthio-1,3,4-thiadiazoles important as diuretics [14-16] and potential anticonvulsants [14-16]. Furthermore, some substituted 5-amino-3*H*-1,3,4-thiadiazole-2-thiones are of interest in photography [17], and as potential anticancer agents [18,19], antibacterial agents [20], and analytical titrimetric agents [21].

Because of the above-mentioned various uses of 5-amino-3*H*-1,3,4-thiadiazole-2-thiones, most of the papers devoted to this group of compounds deal with their synthesis while very little is known about their reactivity. In the present contribution, we wish to report the results of our acylation studies of 5-amino-3*H*-1,3,4-thiadiazole-2-thione (**1**) leading to 5-aroylamino-3*H*-1,3,4-thiadiazole-2-thiones **2**. Only two 5-acylamino-3*H*-1,3,4-thiadiazole-2-thiones have been described in the literature: 2-acetamido-5-mercapto-1,3,4-thiadiazole (**2a**) [18] and 2-benzamido-5-mercapto-1,3,4-thiadiazole (**2b**) [22] (the tautomeric forms of the corresponding thiones). 5-Amino-3*H*-1,3,4-thiadiazole-2-thione (**1**) and 5-aroylamino-3*H*-1,3,4-thiadiazole-2-thiones (**2**) can exist in two tautomeric forms - a thione form and a thiol form as shown in Scheme 1. It is of importance to determine the stable tautomeric structures of these compounds - not only in order to understand their reactivity but also to establish correct names for these compounds. Because ^{13}C nmr spectroscopy represents an efficient tool for distinguishing between a thione form and a thiol form in heterocyclic thiols capable of thiol-thione tautomerism [23-26], ^{13}C nmr spectra and additional experimental information were used to determine the stable tautomeric forms of 5-aroylamino-3*H*-1,3,4-thiadiazole-2-thiones.

2-Benzamido-5-mercapto-1,3,4-thiadiazole [22] was synthesized by cyclization of 1-aminothiocarbamoyl-4-benzyl-3-thiosemicarbazide. The acylation of 5-amino-3*H*-1,3,4-thiadiazole-2-thione (**1**) can take place in two positions, 2 and 5 [22]. To get a 5-aroylamino-3*H*-1,3,4-thiadiazole-2-thione (**2**), the reaction conditions have to be such that only the 5-amino group undergoes acylation.



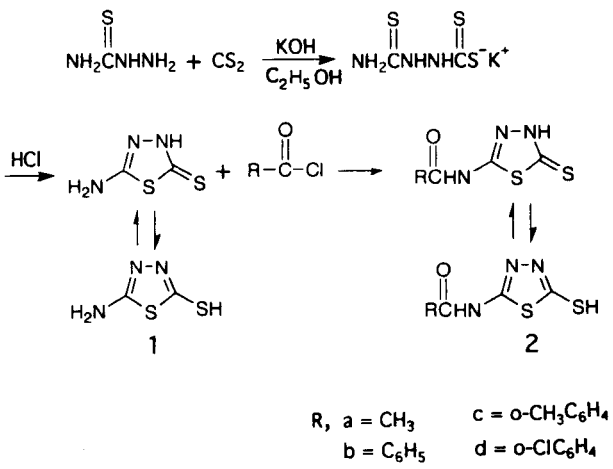
1 2

Results and Discussion.

The new 5-aroylamino-3*H*-1,3,4-thiadiazole-2-thiones **2** were synthesized as shown in Scheme 1.

The starting compound, 5-amino-3*H*-1,3,4-thiadiazole-2-thione (**1**), was obtained by a modified procedure described in the literature [27,28]. Potassium hydroxide was used instead of sodium carbonate and the reaction mix-

Scheme 1



ture was refluxed for 6 hours. The changes resulted in an improvement of the yield to 78%. The ir spectral data and the melting point of our product were identical with those reported by Kurzer [22].

Kurzer's benzoylation [22] of 5-amino-3*H*-1,3,4-thiadiazole-2-thione in pyridine produced not only 2-benzamido-3*H*-1,3,4-thiadiazole-2-thione (**2b**) (yield 52%) but also 2-benzamido-5-benzoylthio-1,3,4-thiadiazole (yield 12%). However, with tetrahydrofuran as the solvent and when the reaction mixture was refluxed for 4 hours with triethylamine used to remove the generated hydrogen chloride, only 5-aroylamino-3*H*-1,3,4-thiadiazole-2-thiones were obtained (yields 80-97% depending on the substituents). 5-Aroylamino-3*H*-1,3,4-thiadiazole-2-thiones **2** are colorless solids. The yields, melting points, and elemental analyses of the synthesized 5-aroylamino-3*H*-1,3,4-thiadiazole-2-thiones **2** are summarized in Table I. The formation of **2**

Table I

Synthesized 5-Acetamido- and 5-Aroylamino-3*H*-1,3,4-thiadiazole-2-thiones **2**

Compound No.	R	Mp, °C [a]	Yield %	Molecular Formula (mol wt)	Analysis Calcd. % C	H	N	Found % C	H	N
2a	CH_3	278-282 [b]	85	$C_4H_5N_3OS_2$ (175.24)	27.42	2.88	23.98	27.54	2.90	24.26
2b	C_6H_5	245-248 [c]	84	$C_9H_7N_3OS_2$ (237.31)	45.55	2.97	17.71	45.69	2.88	17.94
2c	o-$CH_3C_6H_4$	248-252	97	$C_{10}H_9N_3OS_2$ (251.33)	47.79	3.61	16.72	47.94	3.57	16.95
2d	o-ClC_6H_4	204-206	82	$C_9H_6ClN_3OS_2$ (271.75)	39.78	2.23	15.46	39.83	2.20	15.40

[a] All compounds were recrystallized from aqueous ethanol. [b] Ref [18] gives mp 253°. [c] Ref [22] gives mp 234-236° for a monohydrate, $C_9H_7N_3OS_2 \cdot H_2O$.

Table II

Spectral Data for 5-Amino-3*H*-1,3,4-thiadiazole-2-thione **1** and 5-Aroylamino-3*H*-1,3,4-thiadiazole-2-thiones **2**

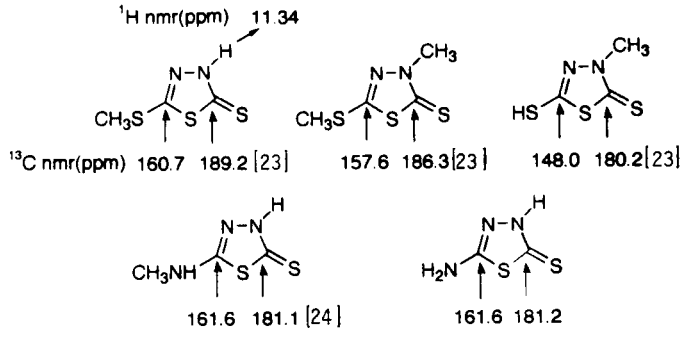
Compound No.	R	IR Spectrum (cm^{-1}, potassium bromide) ^1H NMR Spectrum (ppm, DMSO-d_6) ^{13}C NMR Spectrum (ppm, DMSO-d_6)
1	–	3340 (NH), 3240, 3130, 2920, 1610 (NH_2), 1555 (NH), 1485 (C=S), 1475, 1365, 1325, 1060 (C=S), 1035 [a] 7.0 (2H, b, NH_2), 13.2 (1H, b, NH) 181.2, 161.6
2a	CH_3	3100-2880 (NH + CH), 1650 (C=O), 1590 (NH), 1490 (C=S), 1300 2.12 (3H, *s*, CH_3), 12.45 (1H, b, NH), 14.0 (1H, b, NH) 183.7, 169.4, 152.2, 22.2
2b	C_6H_5	3200-3050 (NH + CH), 1650 (C=O), 1550 (NH), 1340 7.4-8. 3 (5H, m, C_6H_5), 12.7 (1H, b, NH), 13.9 (1H, b, NH) 184.0, 165.7, 153.0, 133.2, 131.0, 128.6, 128.4
2c	o-$CH_3C_6H_4$	3150-2910 (NH + CH), 1680 (C=O), 1560 (NH), 1310 2.4 (3H, *s*, CH_3), 7.2-7.8 (4H, m, C_6H_4), 12.5 (1H, b, NH), 13.9 (1H, b, NH) 183.8, 167.9, 152.4, 136.5, 132.7, 131.2, 130.9, 128.2, 125.7, 19.5
2d	o-ClC_6H_4	3170 (NH), 3030 (CH), 2850, 1640 (C=O), 1550 (NH), 1440, 1300 7.4-7.9 (4H, m, C_6H_4), 12.7 (1H, b, NH), 13.7 (1H, b, NH) 184.0, 165.4, 151.9, 133.1, 132.4, 130.4, 129.6, 127.2

[a] Ref [22] gives 3470 (H_2O), 3195, 2950, 1680, 1645, 1605, 1570, 1510, 1485, 1470, 1320, 1265, 1070, 900, 770, and 685 cm^{-1}.

was confirmed on the basis of ^{1}H nmr, ^{13}C nmr, and ir spectra and the elemental analyses (Table II). In the ^{1}H nmr spectra the disappearance of NH_2 (7.0 ppm) present in the original 5-amino-3*H*-1,3,4-thiadiazole-2-thione (**1**) and the appearance of amidic NH at 12.4-12.7 ppm [2,3] can serve as a supporting evidence for acylation of **1** to **2**. Also, amidic functional groups are clearly present in the ir spectra, with carbonyl stretching at 1640-1680 cm^{-1}, and in the ^{13}C nmr spectra, with the amidic carbon at 165.4-169.4 ppm. Furthermore, the elemental analyses of the new compounds **2** were in a good agreement with the proposed structures (Table I). Table I includes the reported melting points for **2a** and **2b**. The melting point of **2a** reported in the literature (253°) [18] is considerably lower than ours (278-282°); however, our elemental analysis was much more satisfactory than the analysis reported by Suiko and co-workers [18]. The melting point reported in the literature for **2b** is for a hydrate (234-236°) [22] rather than for a sample without water (245-248°; this work).

To determine the structures of the stable tautomers of 5-aroylamino-3*H*-1,3,4-thiadiazole-2-thiones **2**, their ^{13}C nmr spectra were measured and examined (Table III). The chemical shifts of C(2) in **1** and **2** are almost the same. They correspond to the typical chemical shifts of a thione carbon atom as shown in Scheme 2. The chemical shifts of C(7) in **2** represent those of a typical heterocyclic amide carbon atom [2,3] if one takes into consideration the substituent group effect. The difference between the chemical shifts of the acetyl carbonyl carbon atom (in **2a**, 169.4 ppm) and the benzoyl carbonyl carbon atom (in **2b**, 165.7 ppm) is between 3 and 4 which is in agreement with the additivity rule for ^{13}C nmr in amides [30].

Scheme 2



The chemical shifts of carbon atoms in the phenyl rings (Table IV) were satisfactorily correlated with the calculated values using the substituent parameters of monosubstituted benzenes, with the C=O(NH) group taken approximately as C=O(NH_2) [31] (Scheme 3).

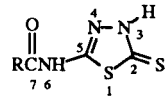
In the ^{1}H nmr spectra, ring NH's are clearly represented as a thioamide NH between 13.2 and 14.0 ppm instead of the aromatic SH [32] which appears at 2.0-4.0 ppm. Thus, one can conclude that 5-aroylamino-3*H*-1,3,4-thiadiazole-2-thiones **2** and 5-amino-3*H*-1,3,4-thiadiazole-2-thione (**1**) exist in their thione form rather than the thiol form in a dimethyl sulfoxide solution.

Table III

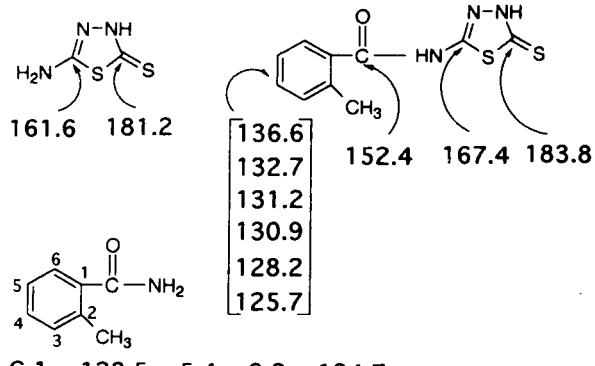
Comparison of the ^{13}C NMR Chemical Shifts for 5-Amino-3*H*-1,3,4-thiadiazole-3-thione 1 and 5-Aroylamino-3*H*-1,3,4-thiadiazole-2-thiones 2 [29]

Compound No.	R	^{13}C NMR Chemical Shifts (ppm, DMSO-d_6) [a]		
		C(2)	C(5)	C(7)
1	–	181.2	161.6	–
2a	CH_3	183.7	152.2	169.4
2b	C_6H_5	184.0	153.0	165.7
2c	o-$CH_3C_6H_4$	183.8	152.4	167.9
2d	o-ClC_6H_4	184.0	151.9	165.4

[a] The numbering of atoms (for compound **1**, the numbering in the heterocyclic ring is the same):



Scheme 3



C-1 = 128.5 + 5.4 + 0.8 = 134.7
C-2 = 128.5 - 0.3 + 9.3 = 137.5
C-3 = 128.5 - 0.9 + 0.8 = 128.4
C-4 = 128.5 + 5.0 + 0.0 = 133.5
C-5 = 128.5 - 0.9 - 2.9 = 126.5
C-6 = 128.5 - 0.3 + 0.0 = 128.2

EXPERIMENTAL

All melting points were determined on an electrically heated Thomas-Hoover capillary melting point apparatus and are uncorrected. The ir spectra were measured on a Jacob A-1 spectrometer. The ^{1}H and ^{13}C nmr spectra were obtained on a 80 MHz Bruker AC-80 spectrometer. Elemental analyses were carried out on a Perkin-Elmer apparatus, model 240, at the Korea Research Institute of Chemical Technology, Daejon, Korea. Most of the commercially available starting materials and solvents were purchased from Aldrich Chemical Company, Milwaukee, WI.

Table IV

^{13}C NMR Chemical Shifts of the Phenyl Ring Carbon Atoms in 5-Aroylamino-3*H*-1,3,4-thiadiazole-2-thiones **2**

Compound No.	R	^{13}C NMR Chemical Shifts (ppm, DMSO-d_6) Found/Calcd [a]					
2b	C_6H_5	133.2	131.0	128.6	128.4		
		133.9	133.5	128.2	127.6		
2c	*o*-$CH_3C_6H_4$	136.6	132.7	131.2	130.9	128.2	125.7
		137.5	134.7	133.5	128.4	128.2	126.5
2d	*o*-ClC_6H_4	133.1	132.4	130.4	129.9	129.6	127.2
		134.6	134.5	134.1	129.2	127.8	125.6

[a] For the method of calculation, see ref [31].

5-Amino-3*H*-1,3,4-thiadiazole-2-thione (**1**).

5-Amino-3*H*-1,3,4-thiadiazole-2-thione (**1**) was synthesized using a modified procedure described in the literature [27,28]. Potassium hydroxide (9.0 g, 0.16 mole) was dissolved in anhydrous ethanol (40 ml) and carbon disulfide (18.3 g, 0.24 mole) was added to the solution. After the addition of carbon disulfide, thiosemicarbazide (13.5 g, 0.15 mole) in anhydrous ethanol (40 ml) was added and the mixture was stirred and refluxed for 6 hours. Most of the solvent was removed under reduced pressure and the residue was dissolved in water (60 ml) and carefully acidified with concentrated hydrochloric acid (15 ml). The precipitate was filtered off to give 5-amino-3*H*-1,3,4-thiadiazole-2-thione (**1**) (15.6 g, yield 78%). The crude product was washed with cold water and the pale yellow solid was recrystallized from ethanol to give the analytical sample, mp 230-232° dec (lit mp 232° dec [27]); ^{1}H nmr (DMSO-d_6): δ 7.0 (2H, b, NH_2), 13.2 ppm (1H, b, NH); ^{13}C nmr (DMSO-d_6): δ 181.2, 161.6 ppm; ir (potassium bromide): ν 3340 (NH), 3240, 3130, 2920, 1610 (NH_2), 1555 (NH), 1485 (C=S), 1475, 1365, 1325, 1060 (C=S), 1035, 755 cm^{-1}.

Acylation of 5-Amino-3*H*-1,3,4-thiadiazole-2-thione (**1**).

5-Amino-3*H*-1,3,4-thiadiazole-2-thione (**1**) (1.33 g, 0.011 mole) was dissolved in tetrahydrofuran (50 ml). Triethylamine (1.51 g, 0.015 mole) and a substituted benzoyl chloride (0.01 mole) were added to the solution and the mixture was refluxed with stirring for 4 hours. Triethylamine hydrochloride was filtered off, the solution was concentrated to one-third of its original volume, and carefully acidified with concentrated hydrochloric acid. The precipitate was collected by filtration and recrystallized from aqueous ethanol to obtain an analytical sample of the corresponding aroyl derivative **2**. The yields, melting points, and spectral data of the products are shown in Tables I and II.

Acknowledgements.

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[29] The ^{13}C chemical shifts in 5-aroylamino-2*H*-1,2,4-thiadiazol-3-ones and their methyl derivatives discussed in one of our previous papers [3] (Table IV in ref [3]) had to be reassigned on the basis of additional ^{13}C nmr measurements on a Bruker AMX-500 500 MHz instrument (also ^{13}C-^{1}H two-dimensional spectra) and by comparison with the data on similar compounds published in the literature [33-37]. The corrected sequence of assignments in Table IV [3] is C(5), C(3), and C(7) [rather than the original sequence which was C(7), C(5), and C(3)]. – The authors wish to thank Prof. Dr. Gerrit L'abbé (Leuven, Belgium) for his suggestions which resulted in corrected assignments.

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